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Comments on the published systematic review and meta-analysis on the increasing antibiotic resistance in *Clostridioides difficile*

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To the Editor

Concerning the published article " Saha, Srishti, et al. Increasing antibiotic resistance in *Clostridioides difficile*: A systematic review and Meta-analysis. Anaerobe 58 (2019): 35–46." [1]. We read this manuscript with interest and found some drawbacks in the categorization of data implementation.

The resistance rate of *C. difficile* to some antibiotics was investigated in this article. Antibiotic resistance data were extracted from reports in the searches of Ovid MEDLINE In Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Web of Science, and Scopus from inception through March 31, 2017 database searches. Eventually, 60 articles were used for the final analysis. Subgroup analysis was performed by study period, continent, antibiotic resistance testing method. Data of ribotype 027 were analyzed separately. There was no mention of quality assessment of the included studies in this meta-analysis. All antibiotic susceptibility testing's (AST) guidelines were grouped as the same category and were analyzed; whereas for some of the antibiotics breakpoints there were variations between AST guidelines (Some of these differences were shown in Table 1) [2,3].

In this study, the reports were used in the Meta-analysis without performing an appropriate quality assessment which means aggregating resistance rate of isolate that do not have a clear origin or has been isolated from a particular section of the hospital. So, the bias risk of the low-quality articles was confirmed. The result, due to inaccuracy in this method, was affected. According to the manuscript, if the articles reported the number of susceptible, intermediate resistance and resistant strains, only the number of resistant isolates was extracted and included. The AST guidelines that were used in these studies, were obtained as a data. Due to the passage, most articles have cited CLSI (27 research) as reference and also some other AST such as EUCAST and etc. Despite extraction from AST guidelines data; unfortunately, the data analyzed in unity, regardless of the differences in the AST guidelines were cited in the papers. Thus, the disparity in the breakpoint was inherent in each AST guidelines, for example, in the case of Metronidazole. The result of AST was presented by EUCAST breakpoint (>2mg/l) as it is different from the result of a report based on CLSI breakpoint (≥32mg/l). They also analyzed articles with another AST breakpoint in a single batch. Therefore, the total resistance values and proportion does not accurately correlate. The results of continental subgroup analysis get an error due to the generality of using particular AST guideline in each continent.

Our recommendation for conducting a systematic review and Meta-analysis in this subject, especially at the global level, primarily, is to develop a suitable questionnaire of quality assessment for the study and perform it accurately. Analyzing the results of the quality assessment as a subgroup to discover the relation between quality of studies on reported resistance rate, in order to identify the risk bias of poor-quality studies. Accordingly, the presence of various AST guidelines causes multiple breakpoints in use. It is advisable to categorize the data according to the reported breakpoint for each piece in order to obtain an accurate antibiotic resistance rate. It should be mentioned that the results of the analysis based on each AST guidelines breakpoint should be categorized separately.

Table 1
Comparing AST breakpoints in EUCAST and CLSI.

Antibiotic	CLSI Breakpoint (mg/l) R ≥	EUCAST breakpoint (mg/l) R >
Tetracycline	16	0.25
Moxifloxacin	8	4
Metronidazole	32	2
Vancomycin	-[a]	2

[a] CLSI hove not vancomycin breakpoint for *C. difficile* and some article used *S. aureus* vancomycin breakpoint (16 mg/l).

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